Acta Medica Okayama

Volume 23, *Issue* 6 1969 *Article* 11

DECEMBER 1969

Dogs refractory to compound 48/80 and sinomenine

Koiti Endo* Hidemasa Yamasaki†

*Okayama University,

†Okayama University,

Dogs refractory to compound 48/80 and sinomenine*

Koiti Endo and Hidemasa Yamasaki

Abstract

Five (21 per cent) out of 24 mongrel dogs were found to be refractory to compound 48/80 and also to sinomenine (cross-tolerance). These nonreactor dogs responded normally to PVP and tween 20 and showed normal sensitivity to histamine. The incidence was similar in both sexes. Mechanisms of this type refractoriness were discussed.

*PMID: 4192963 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **23**, 589—592 (1969)

DOGS REFRACTORY TO COMPOUND 48/80 AND SINOMENINE

Koiti ENDO and Hidemasa YAMASAKI

Department of Pharmacology, Okayama University Medical School, Okayama, Japan
(Director: Prof. H. Yamasaki)

Received for publication, July 14, 1969

WEST and HARRIS (1, 2) secured rats, from one Wistar albino colony, resistant to the first injection of dextran or egg-white, failing to develop the so-called anaphylactoid reactions, and they showed further that this nonreactivity was an autosomal recessive character. But we have yet no information concerning naturally or congenitally resistant individuals to histamine liberators or histamine-releasing agents in other species of animal. Fifteen years ago, MAYEDA (3) working in this laboratory on the histamine-releasing properties of a plant alkaloid, sinomenine, found unexpectedly that 11 (14 per cent) out of 78 dogs were refractory to the depressor action of this histamine liberator. We again noticed, during the course of recent work, that some dogs were nonreactive to the hypotensive actions of both compound 48/80 and sinomenine, that is, they were cross-tolerant to either liberator. This brief account concerns with experiences on these nonreactor dogs.

Observations were made on 24 mongrel dogs in either sex (13 males and 11 females), whose carotid blood pressures were recorded on a smoked drum by means of mercury manometer under anesthesia by intravenous injection of pentobarbital sodium 35 mg/kg. Eighteen dogs (9 males and 9 females) weighing 7.5 to 18.5 kg were injected 0.7 to 1.0 mg/kg doses of compound 48/80 intravenously. Fifteen dogs among them showed a typical reaction of rapid and profound fall of the arterial pressure, reaching the maximal fall of 71 to 84 per cent, except one who died from a severe shock by 0.7 mg/kg of 48/80 about 5 minutes after the injection. But, to our interest, other 3 dogs (one male, 9.2 kg; 2 females, 12 and 13.5 kg) were completely refractory to the first injection of mentioned doses of 48/80, and these dogs were also unresponsive to the following injection of 3 mg/kg, a shock dose, of sinomenine hydrochloride (Fig. 1).

Another group of 6 dogs (4 males and 2 females), weighing 5.5 to 12.6 kg, were received the first intravenous injection of 3 mg/kg of sinomenine hydrochloride. Among them 4 dogs reacted normally with a steep

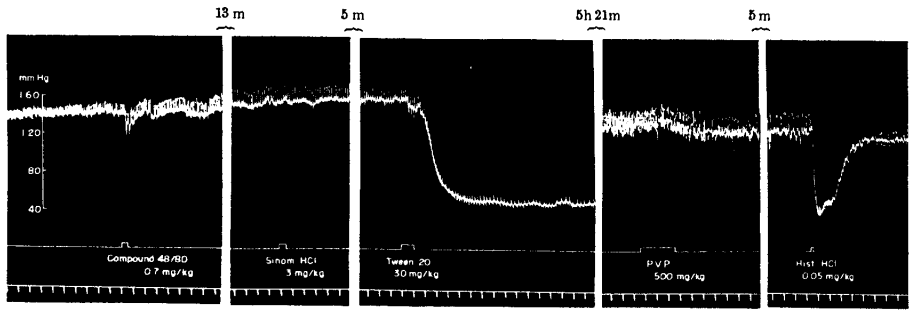

Fig. 1. Carotid blood pressure of a dog refractory to compound 48/80 and sinomenine. A marked hypotension was produced by a subsequent intravenous injection of tween 20, although after this a shock dose of PVP was no longer effective probably being due to exhaution of releasable histamine stores. Normal sensitivity to histamine is shown. Dog, 13.5 kg female.

and marked hypotension, showing the maximal fall ranging from 68 to 91 per cent, but remaining 2 dogs (both males, 9.8 and 10.5 kg) were not only entirely refractory to the sinomenine injection, but also failed to show any depressor reaction to 1.0 mg/kg of compound 48/80 injected about 10 minutes later.

Dogs who had been proved to be refractory to 48/80 and sinomenine were injected intravenously either polyvinylpyrrolidone (PVP) 500 mg/kg or tween 20 30 mg/kg. These nonreactor dogs now reacted normally to either histamine-releasing agent, showing a marked hypotension, although after the recovery renewed injections of both PVP and tween were no longer effective. Histamine was as active as in control dogs (Fig. 1).

It will be seen that the percentage of nonreactor dogs (21 per cent, 5 out of 24) was similar in both sexes (male 23 per cent, 3 out of 13; female 18 per cent, 2 out of 11) and did not vary from body weight to body weight within the ranges in the present experiments.

An important element in the development of refractoriness to histamine release is the exhaution of the releasable histamine stores. But, this is the cause improbable in the present refractoriness to 48/80 or sinomenine, since the nonreactor dogs responded with conspicuous hypotensions to PVP or tween 20 which are both known histamine-releasing agent specific to this animal. SLOMKA and GOTH (4) succeeded in dogs to produce a refractory state to compound 48/80 by injecting a series of graded doses of this compound, and they considered this refractory state to be effected by a mean other than depletion of available histamine stores. KOMOTO and YAMASAKI (5) confirmed this finding, and further successfully secured sinomenine-resistant dogs by a similar technique, repeating injections of a series of

increasing doses starting with a very small dose of sinomenine. They found that these dogs were also endowed with the refractoriness to the hypotensive effect of compound 48/80. Since no increase in plasma histamine was seen after each injection during the treatment and also the histamine content in the skin remained unchanged after the refractoriness was established, this refractoriness might not be the result of exhaution of the releasable histamine in the body stores. RILEY and WEST (6, 7) have made the interesting observation that with long-continued administration of compound 48/80, the reduced histamine content of rat subcutaneous tissue begins to rise again slowly, accompanied by the appearance of small dense new mast cells in close relation to the blood vessels, cells which now resist degranulation by 48/80. All these observations seem to make it possible that mast cells can be made resistant to certain types of histamine liberator.

What is the mechanism by which this can be achieved? There are two possibilities that can be considered: one is the lack or masking of the receptors for the histamine liberators postulated in the surface membranes of mast cell; another is the deficient or inability of the element(s) necessary to the enzymatic processes involved in the histamine release mechanisms in mast cells. Recent observation (8) that toluidine blue disrupts mast cells before entering into the cytoplasmic milieu seems favorable for the receptor concept. This receptor theory also favorably permits explanation of the cross-tolerance for compound 48/80 and sinomenine since these compounds are chemically simple bases and of close similarity in their modes of action on mast cells (9, 10). Whether the present refractoriness is naturally acquired or hereditarily controllable, should also be a matter of interest to be followed.

SUMMARY

Five (21 per cent) out of 24 mongrel dogs were found to be refractory to compound 48/80 and also to sinomenine (cross-tolerance). These non-reactor dogs responded normally to PVP and tween 20 and showed normal sensitivity to histamine. The incidence was similar in both sexes. Mechanisms of this type refractoriness were discussed.

REFERENCES

1. HARRIS, J. M. and WEST, G. B.: Anaphylactoid reaction in rats. *Nature, Lona.* **191,** 399—400, 1961
2. WEST, G. B. and HARRIS, J. M.: Pharmacogenetics—A fresh approach to the problem of allergy. *Ann. N. Y. Acad. Sci.* **118,** Art. 8, 439—452, 1964
3. MAYEDA, H.: The release of histamine by sinomenine. *Jap. J. Pharmac.* **3,** 62—72, 1953

4. SLOMKA, M. B. and GOTH, A.: Some observations on nature of refractoriness to histamine liberators. *Proc. Soc. exp. Biol. Med.* **93**, 30—32, 1956
5. KOMOTO, S. and YAMASAKI, H.: The sinomenine tolerance without histamine depletion. *Folia pharmac. japon.* **63**, 147§, 1967 (in Japanese)
6. RILEY, J. F. and WEST, G. B.: Histamine liberation in the rat and mouse. *Archs int. Pharmacodyn. Thér.* **102**, 304—312, 1955
7. RILEY, J. F. and WEST, G. B.: Tissue mast cells. Studies with a histamine-liberator of low toxicity (compound 48/80). *J. Path. Bact.* **69**, 269—282, 1955
8. KOMOTO, S. and YAMASAKI, H.: The mechanism of histamine release by toluidine blue from isolated rat mast cells. *Folia pharmac. japon.* **63**, 146§, 1967 (in Japanese)
9. SAEKI, K.: Effects of compound 48/80, chymotrypsin and anti-serum on isolated mast cells under aerobic and anaerobic conditions. *Jap. J. Pharmac.* **14**, 375—390, 1964
10. YAMASAKI, H. and SAEKI, K.: Evidence for energy-requiring processes in mast-cell degranulation and histamine release in rat induced by sinomenine. *Proc. Japan Acad.* **41**, 958—962, 1965